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Abstract	Abstract

Background: Massive strides have been made with respect to primary and secondary prevention of human papillomavirus (HPV)-associated disease as a result of prophylactic vaccination and cervical screening based on molecular HPV testing. However, cervical cancer continues to be an important clinical and societal burden. Additionally, other HPV-associated cancers for which there are no screening programmes are rising. Finally, the optimal combination of vaccination and screening strategies will require careful thinking. Considering this unprecedented and important time, we were keen to solicit the views of the expert community to determine what they perceived were the key priorities for HPV research. Our objective was to identify consensus and key priorities for HPV-based research through provision of a questionnaire disseminated to a multidisciplinary group of key opinion leaders (KOLs).

Summary: A structured survey composed of 46 HPV research “categories” was sent to 73 KOLs who were invited to “rank” the categories according to priority. The invitees represented clinical and public health disciplines as well as basic scientists. Scores were weighted according to the number of responses. Invitees also had the opportunity to comment on barriers to the research and suggest other research areas that required attention not reflected in the survey. We received 29 responses in total; overall, the 3 highest-ranked categories were “optimal cervical screening in low and middle-income countries (LMICs),” “primary disease prevention in LMICs” and “impact of vaccine on HPV infection and associated disease.” “HPV and the microbiome” and “mechanisms of transformation” were the highest-ranked categories with

respect to basic research. Consistent barriers to research were around governance on the use of samples and data and funding, particularly in an era of vaccination. **Key Messages:** Research to support the management of disease in LMICs is clearly perceived as a priority in the international community in addition to other diverse areas which necessitate an improved basic understanding of viral mechanisms and interactions. International, multidisciplinary efforts which articulate the broader HPV research agenda will be important when seeking funding in addition to international endeavours to support the efficient use of existing samples and cohorts to facilitate such research.

Abstract Second Language	

Abstract Third Language	

Key Messages	

Body

Introduction

Unquestionably, this is an important and almost unprecedented time for human papillomavirus (HPV)-based research. Decades of ground-breaking work starting with the demonstration of a transmissible agent that could cause warts led to the confirmation that certain carcinogenic (high-risk) HPV types can cause cervical cancer [1–3]. More recently the research has translated into global primary and secondary disease prevention strategies, which

increasingly depend on HPV-based vaccination and testing [4]. In synch with such developments, laboratory technology/ies have advanced dramatically; molecular detection strategies have ostensibly replaced “direct morphology-based identification” and themselves have evolved from straightforward detection of single target(s) via PCR into next-generation platforms with massive resolving power that can rapidly detect whole viral genomes and sequence the host genome which HPVs occupy [5, 6].

Are we nearing the end of the road for HPV research? Have we made all reasonable endeavours to address this area, and should we focus our resolve and energies on alternatives, particularly now that we are seeing the impact of vaccination on such a scale? We would argue otherwise. Unfortunately, cervical cancer still continues to be a major clinical and societal burden, particularly in low and middle-income countries [7]. Additionally, other HPV-associated cancers for which there are no screening programmes are rising, including but not confined to oropharyngeal cancer [8, 9]. We do not have a clear idea about mechanisms of HPV persistence versus clearance and the precise molecular details of how certain hrHPV types can lead to cancer, sometimes in a short time frame. Relatively little is known about the specific genetic and epigenetic mutations that underpin the evolution of cervical intra-epithelial neoplasia (CIN) 3, nor exactly which steps have a required sequence that then further facilitate the transformation of CIN3 to malignancy [10, 11]. In addition, the optimal combination of vaccination and screening strategies will require agile thinking so that the value and efficiency of both can be realised in a time where shifting patterns of infection and disease will be the norm.

A Survey to Help Define the Key Priorities for HPV Research for the Next 5–10 Years

Rather than simply stating “more work/research is needed” one of the aims of this piece was to try to identify priorities for HPV research going forward in the next 5–10 years at this

crucial time. To inform this we constructed a structured survey composed of 46 HPV research "categories" (Fig. 1) which was sent to key opinion leaders (KOLs) who were invited to "rank" the categories according to what they perceived as a priority (Table 1), with 1 being highest and 10 being lowest priority. The invitees represented various professions as summarised in Figure 2. Invitees were also offered the opportunity to comment on what they considered could be barriers/issues to the research and were also given the opportunity to suggest other research areas that required attention which were either not included or adequately reflected in the survey-wording.

Dissemination

The initial survey was first sent to a "pilot" panel of individuals representing the above disciplines. The pilot panel offered key feedback/suggestions, which informed subsequent dissemination of a finalised questionnaire to 73 KOLs.

Response(s) to Research Questionnaire

We received a total of 29 responses; 25 of the surveys were utilisable for scoring, and the remainder were used descriptively for specific comments.

We received responses from all 7 of the "disciplines" described earlier although those from epidemiologists, clinicians (particularly gynae-oncology) and basic virology were the most represented. The majority of responses were from KOLs based in North, South or Central America or Europe. Responses from those with particular expertise in conducting research in low- to middle-income countries (LMICs) were also obtained.

Of the 46 categories in the survey we present those that were ranked as the first 15. Arguably, the first 15 categories can be grouped into three themes: (1) cervical screening, (2)

vaccination, (3) basic science and biobanking (Fig. 3). In the subsequent sections we discuss priorities in relation to the said themes.

As not all responders added a score to each category, scores were weighted according to the number of responses.

Cervical Screening

The category considered the highest research priority was "*optimal cervical screening in LMIC*" although it was of interest that two further categories based on cervical screening research ranked within the top 5: *"optimal cervical screening in high-income countries (HICs)"* and "*optimal screening strategies for vaccinated women.*"

Other top 15 categories related to screening included: *"self-sampling to support cervical screening and disease management," "improving equity of access in cervical screening"* and *"quality assurance and metrics for HPV-based screening."*

With respect to the "top" priority a general barrier to delivery was inevitably "funding" in addition to responses that modelling studies will continue to be of value given the practical challenges of performing active research. It is beyond the scope of the present manuscript to consider all of the potential options for LMIC particularly given that one solution will clearly not "fit" all needs. However, one issue that will require careful consideration is the optimal combination of vaccination and screening with this representing a challenge for all settings. The aspiration of the HPV FASTER endeavour/group is based on the proposal of extending HPV vaccination programmes to women up to the age of 30 years (and potentially up to 50 in certain settings) in addition to at least one HPV-based screening test in women aged 30 or more [12]. Various modelling studies based on actual and anticipated reduction in viral and disease prevalence have converged on the conclusion that cervical screening of immunised women may involve 2–3 visits in a lifetime [13–15]. The Australian COMPASS trial will represent the first randomised controlled trial of HPV primary screening versus cytology in a population that includes females with high vaccine uptake rates [16]. While these conclusions will be of

undoubted and timely value to the international community, how easily the observations may be extrapolated and transcribed may be more challenging given: (1) the significant variability in cytology performance between and within countries, (2) the potential impact of HPV primary screening assay choice, and (3) immediate and subsequent triage strategies which again vary widely according to programme [17]. Thus, requirement for country-specific evaluation projects which take into account mixed populations of immunised and non-immunised women may be justified. Such projects are also likely to benefit from the incorporation of modern technologies related to sample taking and laboratory testing.

Self-sampling based on the dissemination of postal testing kits, which contain swabs for the self-collection of exfoliated vaginal samples, has been introduced in certain settings, including at the programme level [18, 19]. Self-sampling has largely been directed to women who default from regular screening invitations [20, 21]. Such work speaks to *"addressing/improving equity of access in cervical screening."* Certainly, the speed of development of self-sampling devices has accelerated considerably over the last 5 years as has the consideration of urine as a credible biospecimen for HPV testing [22–24].

There are fewer studies that have directly addressed the performance of self-sampling in those who do attend for cervical screening [25]. Given the accelerated progress in objective molecular triage strategies (see later), which could obviate the requirement to visit a clinic, this is arguably an under-researched area both with respect to attitudinal research and "wet," cohort studies or trials. Hurdles identified by the KOLs to delivering this type of research include engagement and buy-in from the gynaecological community given that it may "reduce their income." This "gynae scepticism" as one KOL put it may be particularly marked in settings with opportunistic screening programmes. Further work to quantify the extent of this scepticism (and its drivers) may be of value and help determine what level and type of evidence would be required to effect an actual change.

Regarding *"biomarkers for risk stratification and triage of HPV infection"* the perceived significant appetite for these in the international community has been borne out by the present survey. However, in terms of application, of the countries which have implemented HPV primary screening programmes (or pilots), the triage strategies imposed have involved cytology (with or without adjunctive staining), limited genotyping or a combination of both [17]. These strategies do not provide a binary (yes/no) answer that allow "triage"-negative women to be returned to routine screening. Additionally, triage strategies based on morphology and limited typing will be less practicable and efficacious given challenges around retention of cytology workforce and the impact of vaccination which will reduce the PPV of both approaches [26, 27]. Further work to develop and apply objective triage tests that do not require subjective interpretation and are unaffected by immunisation are warranted. The most evidenced candidate(s) are assays that are based on viral and/or cellular methylation. Methylation testing may be an effective triage tool to detect and characterise women at high risk of developing CIN3. The effectiveness of such tests in predicting CIN3 may influence the screening process in many ways, for example by providing an objective method to reach more accurate prognoses or by helping to avoid overtreatment of women with non-progressive lesions [28–31].

When considering *quality assurance and metrics for HPV-based screening*, this is a very translational aspect but one that does require attention. The frequently cited guidelines of Meijer et al. [32] from 2009 have been invaluable for the benchmarking of HPV DNA tests that are suitable for cervical screening. However, the guidelines are nearly 10 years old and omit certain elements that would be required for contemporary screening practices such as consideration (and relevant validation) of genotyping tests, biomarker tests, self-sampling and the influence of vaccination. Other key aspects of quality monitoring must incorporate performance of the test and subsequent management algorithms relative to significant disease within a programme, according to the accepted standards/key performance indicators. Again, as the pattern and extent of disease change in countries where vaccination has been embedded, these

performance indicators may well need to adapt. Suggested barriers to this type of research included “getting the health care services to understand that quality assurance is important” and issues around the accuracy/comprehensiveness of relevant data sources, access therein and governance, which again may be more challenging in opportunistic programmes.

Vaccination

“Primary disease prevention in LMIC via prophylactic vaccination (including 1-dose schedules)” was the second highest rated of the categories/priorities described and is in line with the highest rated category *“optimal cervical screening in LMIC.”* The reality that 80% of cervical cancers are diagnosed in LMIC explains this observation. Twelve years ago, when a number of HICs were introducing HPV vaccine programmes there was a vanishingly small number of LMICs that were doing the same, largely due to cost of the vaccine which may have been compounded by the Global Alliance on Vaccines and Immunisation (which supports funding of childhood vaccination programmes in LMIC) not committing resources until 2011 [33–35]. In 2018, the situation is more encouraging; a greater number of LMICs now have HPV demonstration projects or programmes and the “73 Decade of Vaccines” countries are projected to deliver HPV vaccine programmes in the period between 2015 and 2030. The endorsement of multicohort vaccination of 9- to 14-year-old girls in LMIC by the WHO could also maximise benefits. Previously, single age cohort administration was the modus operandi for LMIC, usually at the lower end of the age indication (9–10 years). However, accumulated evidence, including that derived from modelling work, indicates that multicohort vaccination could bring about a reduction in cervical cancer deaths at a greater rate, as recently described [36]. The utility of 1-dose schedules has also been demonstrated in post hoc evaluations of the vaccine trials and in disaggregated data from national programmes (where available) although efficacy has been largely shown for viral rather than disease end points [37]. The recent set-up of prospective randomised controlled trials which will directly address the effectiveness of reduced dose schedules will be of clear value and is likely to influence decision making given the cost and

logistical savings [38, 39]. This is relevant when we considered the respondent issues to barriers around vaccination which included “funding,” “governance” and “competing priorities.”

It was also notable that “impact of vaccine on HPV infection and associated disease” was considered a top-5 priority, irrespective of setting. While considerable data are now available which have shown a significant impact on a variety of different outcome measures (infection, warts, herd immunity, clinical activity) [40–42] we still await data to demonstrate impact on cancer and also direct evidence from mixed dosing trials (where different vaccines have been used in schedules of >1 dose). The demonstration of vaccine efficacy links to *“management and mitigation of perceived vaccine safety issues.”* Arguably such a demonstration (including in LMICs) is key to supporting positive and evidence-based messages around the benefits-to-harms ratio of the vaccines. The republic of Ireland experienced a significant drop in uptake (from around 87% in 2014 to approx. 50% in 2016/17) after heavyweight antivaccine lobbying, although recent evidence indicates that rates are now recovering [43]. However, this was after significant effort and explicit government support which included the creation of the HPV Vaccination Alliance, a group of approximately 35 separate diverse organisations, including women’s rights, child welfare and various health organisations, all committed to raising awareness of HPV vaccination. The experience in Ireland and indeed elsewhere (including Denmark, Romania and Japan) [44–46] shows how rapidly successful campaigns can founder and strengthens the case for applied high-quality research that “explores barriers to vaccine participation.” Consistent feedback from KOLs on the hurdles of delivering such information was based around the challenges and governance of gaining access to unvaccinated females (in various settings) with whom to conduct qualitative research. A further interesting comment was that for traction, the results of such studies required “acceptance by biologic scientists and physicians of results and implementation plans.”

Determination of vaccine effectiveness includes gaining a greater understanding of “immunogenicity and long-term protection” in order to inform pragmatic strategies/schedules

going forward and to support key educational messages to best engage the public. However, consistent with feedback, ease of delivery will vary according to setting. Countries with centralised cancer registries and national cervical screening databases where accurate immunisation data can be linked (with due process of governance) to other relevant health care data sets are in the minority including in HICs. Potentially, the creation of “international databases” (to quote from one KOL) that could be “used to determine health disparities” and determine differential impacts on particular ethnic and societal groups would be of value. Like many other categories, research exploring the impact of and barriers to vaccination was perceived to be hampered by lack of funding. While industry has played a crucial part in supporting and funding long-term efficacy and safety trials, the conflict that this presents, particularly to the antivaccine community, can limit and subvert the conclusions of these studies. One responder indicated that “ideally studies must remain absolutely free of conflicts to assure trustworthiness.”

Therapeutic vaccination was also included in the first 15 categories. While clearly of value there is to date no licensed therapeutic vaccine or antiviral that carries a specific indication for HPV-associated disease. Therapeutic vaccines may be based on live vectors, protein/peptide, whole cell(s) or nucleic acid. An increasing number of vaccines have now reached clinical trial/application, most prominently for nucleic acid-based vaccines. Encouraging results in phase 2 clinical trials have been observed in patients with HPV16- and HPV18-associated CIN and also in vulval disease [47]. In addition to the generation of new candidate therapeutic vaccines and assessment of their efficacy in trials, several strategies that could enhance the vaccine effect require investigation. Such strategies need to include improvement in the uptake and presentation of HPV antigens in dendritic cells [48, 49]. Furthermore, optimal use of a vaccine in combination with other therapies including chemo-radiotherapy and immunological adjuvants is an area that would benefit from additional research and is consistent with the general endeavour in health care to deliver personalised/stratified management for

patients [47, 50, 51]. There was a relatively small amount of feedback related to challenges around delivering research to develop this particular field although 2 respondents indicated the importance of performing basic science to understand and define the key immunological effectors of disease regression, as well as robust clinical trials. These comments are consistent with those articulated in an excellent review of therapeutic vaccines by Cheng et al. [47], who stated that “a deeper knowledge of the tumor micro-environments also holds great potential for improving therapeutic vaccines.”

Basic Science and Biobanking

The aspect of basic science relating to HPV which was considered the highest priority was *molecular and cellular biology – transformation.* Key effectors and players critical to the transformation process are challenging to trial in patient settings as the threshold for treatment is generally CIN2+, a heterogeneous lesion, the majority of which will regress and as discussed more than half of CIN3 (a greater proxy of significant disease) will regress [52]. Models to study HPV infection and transformation are clearly important, thus the development and access to such models are crucial to understanding basic mechanisms key to viral life cycle and transformation, in addition to helping to determine the influence of external agents/therapeutics. The development and enhancement of model systems was identified as a missing priority area in the survey. Creating such models is challenging as HPV is obligated to complete its life cycle in human differentiated epithelium which is clearly complex to recreate. The most established models involve the culture of HPV-infected keratinocytes, directly derived from a human lesion (e.g., W12) or transfected artificially (e.g., NIKS) in organotypic raft cultures. Raft cultures enable epithelial differentiation to be capitulated at least to an extent in vitro [53, 54]. These systems have been used extensively although with a bias to those infected with HPV16 and HPV18.

Animal models arguably offer a more holistic system in which to monitor infection and disease longitudinally, particularly given the natural history of lesion development which can take several years and the fundamental influence of immune responses. The cottontail rabbit papillomavirus and the rabbit oral papillomavirus have yielded important discoveries including insights into the features/hallmarks of viral latency and how this links to clinical manifestations [54]. The mouse papillomavirus MmuPV has also been used recently to study the influence of immunological factors on HPV infection and associated lesions, and transgenic models of disease have provided insights into the influence of external factors such as hormones and UV irradiation on disease [55]. Compared to models of cervical disease, models of other HPV-associated cancers are rarer and less established. Given the increase in non-cervical cancers, this is an area that requires attention as was pointed out by a survey responder.

The influence of the microbiome on a diverse range of health outcomes including physical and mental health has been one of the most fertile and interesting areas of microbiological research in the last decade. In relation to HPV infection, data indicate that diversity in the vaginal mucosa is independently associated with a lower risk of disease progression, whereas a reduced relative component of lactobacilli and domination of strict anaerobes is associated with worse outcomes [56, 57]. Lactobacilli support an acidic vaginal environment and studies, including large population-based series, have indicated that low vaginal pH (<5) is associated with a lower risk of HPV positivity. Additionally, Motevaseli et al. [58] showed that lactobacilli can exert a cytotoxic effect on Hela cells (cancer cell line driven by HPV18) independently of lactate and also pH, an effect not observed in a “normal” non-infected epithelial cell line, suggesting that other factors in addition to pH may add protective characteristics of lactobacilli. Such observations have been reinforced by more recent work which demonstrated the inhibitory effect of lactobacillus supernatants on CaSki cells (a cancer cell line which contains HPV16) [59]. This work has brought about consideration of probiotic and prebiotic preparations to modify the vaginal microbiota; the future application of these ideas in

trial settings will provide essential clinical data as to the effectiveness of the approach. The bulk of studies which have assessed the influence of the wider microbiological context and HPV have focussed on the vagina and implications for cervical disease. There are relatively few data that have looked at the microbiome to determine its potential influence on other HPV-associated cancers including oropharyngeal cancer. This may well be an area that deserves increased attention given that small, proof-of-concept studies indicate that the composition of the salivary microbiome may reflect discrete clinical and aetiological states [60]. Few issues with respect to the microbiome were raised by KOLs other than a call to define the term “microbiome” in a bid for accuracy and consistency and to make between-study comparison more robust.

“Access to samples and optimal biobanking for the future” was identified as a priority area, and fundamentally well-annotated biobanks with access to clinical data will support the various research priorities discussed above. Issues raised included “maintenance” and “costs.” Additionally, storage and manipulation of routinely taken clinical samples to deliver research that demands high-quality RNA can be challenging. Consequently, research which supports the enhancement of sample stability and maximal yield and quality of derivatives is important to make the best use of biobanks in the future. International sharing of best practice and protocols will also be of value in achieving this.

Ensuring appropriate and robust governance is in place also absolutely essential, and it can take time to identify and secure the relevant permissions, particularly as there are generally a number of entities who must be engaged with in addition to the research ethical committee. As the set-up of biobanks requires considerable infrastructure, core funding to support this even for a fixed period is of help. Thereafter, revenue can be generated as a function of requests for access to samples. While this can help sustain archives, it is not generally sufficient for complete maintenance, particularly as the frequency and nature of requests cannot be accurately predicted. Complimentary funding from grants is often required as well as core funding from national resources. One issue raised with respect to the latter is the potential lack

of “political awareness” of the requirement for biobanks. Basic and applied studies would benefit from access to well-annotated samples from the cervical screening programmes with long-term follow-up information which would allow an accurate evaluation of new markers and associated interventions. Another added benefit of access to such samples/information would be the potential to link to records that allow the influence of the marker/modality under study on a variety of HPV-related (or putatively related) cancers. Certainly, given the increase in self-sampling in the current screening programmes, biobanks that contain a heterogeneity of both clinician and self-taken samples would be valuable including those from studies where matched samples (clinician vs. self) have been collected. International efforts to support both hard protocols (specimen manipulation) and soft protocols (linkage and governance considerations) for prospective biobanking could be game changing with respect to the speed of how new developments are assessed and implemented [61].

Additional Areas for Research

Table 2 summarises the additional comments we received from responders (*n* = 7) as to “other suggestions for the future.” These areas were perceived as either absent from the original questionnaire or not covered explicitly enough. A total of 14 suggestions were articulated: 3 related to screening, 6 vaccination and 5 addressed to basic science/biobanking. Regarding screening, 2 of the 3 comments, again, described the requirement to deliver research that would support improvements in LMICs. The final comment related to a screening test for oropharyngeal cancer, and this indeed reconciles with the significant global increase in oropharyngeal cancer in the last decade [8]. An “early warning” test for what can be a highly morbid disease is clearly worth consideration; however, one of the challenges around this is the nature of the intervention in view of a positive test, given that there is no clear precursor phase for oropharyngeal squamous cell carcinoma.

The additional comments on vaccination talk to some of the earlier discussion around the requirement for more readily affordable vaccines and associated dosing schedules to support use in LMICs, as does the delivery of research to improve vaccination rates by focussing on behavioural interventions. Research into the use of vaccine for broader/off-label indications was also suggested by 2 separate responders including for “older” age groups and for those potentially at greater risk of disease including those previously treated for high-grade CIN, men who have sex with men and “underscreened” populations. Arguably some of these research proposals have already translated into implementation, for example, in the UK a targeted vaccination programme for MSMs was piloted initially in 2016 with full implementation in place in Northern Ireland, Scotland and Wales. Furthermore, vaccination of older age groups is consistent with the ethos of HPV FASTER, as described earlier [12]. Any potential therapeutic benefit of the prophylactic vaccine would benefit from further comprehensive research as current evidence is relatively ambiguous and largely based on single-arm, small observational trials. The comments on additional developments for basic science spoke to the requirement for specific sample sets to be accommodated in biobanks and the use of models, including models of non-cervical disease to support the identification and assessment of new therapies.

Concluding Remarks

Research on HPV has exerted a significant global impact on the burden of infection and disease in addition to providing insight into key mechanistic processes fundamental for lesion and cancer development that have a broader reach.

The multidisciplinary nature of research to date has undoubtedly contributed to these outcomes. While we have argued that requirement for further HPV research is essential to improve morbidity, globally how to address funding constraints will be an inevitable challenge. An interesting refrain from a number of responders was that strategically, funders may be less

inclined to fund HPV research given the availability and success of vaccine – this was perhaps articulated most succinctly by the comment that “the funding crunch is to some extent a reflection of our own success.” The case for continued funding for HPV-based research requires concerted support from the international community to ensure it does not slip from the agenda and so that opportunities for successful collaborations are identified. Such collaborations may not just be confined to practical projects, but also exercises that make the most of existing sample and data sets. While there are clear governance constraints and processes that are required to permit this, the said processes should balance the potential harms to benefits in order not to preclude or significantly delay relevant contemporary research that will directly inform the next stage of service improvement. As one responder put it: “Arguably, HPV research has been one of the most successful areas in medicine and public health” – now we must be careful not to drop the ball or to throw obstacles in its path.

Finally, while we happily acknowledge the theme of this issue, to contextualise the developments in HPV research, with respect to geological timescales is challenging given that within the three million year quarternary period, the time of humankind is too diminutive to be visible! However, if we refine our perspective to the Jurassic age, perhaps we should reflect that the “dinosaur renaissance,” a revolution which started in the late 1960s, inspired concerted and renewed interest in dinosaurs within academia and popular culture after sight of evidence which indicated dinosaurs may have been warm-blooded, intelligent active animals, rather than plodding cold-bloods as had been the earlier consensus. The said renaissance brought about a seismic shift in thinking on all fundamental aspects of dinosaur biology. Researchers of a certain vintage take heart (!) and positive ownership of the dinosaur epithet to exert your warm-blooded intelligent active selves to meet the challenges of the new epoch in HPV research.

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Author Contributions

K.C.: involved in survey construction and initial testing, survey dissemination, response collation and manuscript preparation and refinement. *A.L.*: involved in survey construction and manuscript preparation, refinement and ultimate review.

B.N.: involved in survey construction and initial testing, survey dissemination, response collation and manuscript preparation and refinement.

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Appendix after References (Editorial Comments)

Legend(s)

Fig. 1. Full questionnaire sent to key opinion leaders.

Fig. 2. Professional “groupings” of the key opinion leaders who responded to the survey.

Fig. 3. The main three research “themes” identified as priorities for development: (1) cervical screening, (2) vaccination and (3) basic science and biobanking.

Table(s)

Footnote(s)

Table 1. Research priorities identified by KOLs (last response June 2018) who were invited to score 46 HPV-related research categories as detailed in Figure 1

Research category	Ranking
Optimal cervical screening in LMICs	1
Primary disease prevention in LMICs via prophylactic vaccination (including 1-dose schedules)	2
Impact of vaccine on HPV infection and associated disease	3
Optimal cervical screening in HICs	4
Optimal screening strategies for vaccinated women	5
Access to samples and optimal biobanking for the future	6
Self-sampling to support cervical screening and disease management	7
Management of (and mitigation against) perceived safety issues with the HPV vaccine	8
Primary disease prevention in HICs via prophylactic vaccination	9
Exploring barriers to vaccination participation	10
Biomarkers for the risk stratification and triage of HPV infection	11
Immunogenicity of vaccines and long-term protection	12
Therapeutic vaccination	13 =
Addressing/improving equity of access in cervical screening	13 =
Quality assurance and metrics for HPV-based screening	14 =
HPV and the microbiome	14 =
Viral molecular and cellular biology – transformation	15

Ranking is based on a total of 25 returned surveys. Categories with the same ranking are shown by the score followed by =. KOLs, key opinion leaders; LMICs, low- and middle-income countries; HICs, high-income countries. The three main research “themes” cervical screening, vaccination and basic science are represented in white, light grey and grey cells, respectively.

Table 2. Additional areas for research perceived by responders as not covered or not comprehensively covered in the questionnaire

Research theme	Comment
Screening	Development of an inexpensive, rapid cervical cancer screening test that could be used in lower-income countries and would be superior to VIA
Screening	Reduction of cervical cancer risk via prophylactic cryoablation of the squamocolumnar junction in low-resource settings
Screening	Development of a screening test for early detection of HPV-related oropharyngeal cancer
Vaccination	Evaluating the efficacy of a 1-dose regimen with nonavalent vaccine
Vaccination	Development of additional HPV vaccines that are less expensive and easier to transport and deliver, which would particularly help low- and lower middle-income countries
Vaccination	Research on public health policy approaches that could mitigate the effects of false attributions of harm associated with HPV vaccination; this would entail both prevention efforts in advance of the roll-out of vaccination and rapid response efforts to limit damage after a false claim has been made
Vaccination	Ongoing behavioural and social science research to develop messaging and behavioural interventions targeted at improving vaccination rates, particularly in countries like the USA that do not have national vaccination policies; this research needs to be multilevel, addressing youth, parents, health care providers, health systems and public health policy
Vaccination	Use of vaccinations at older ages to change screening strategies for older (uninfected) women
Vaccination	HPV vaccines in high-risk groups of adult women and men such as women previously treated for high-grade CIN, immunocompromised women and men, MSM and underscreened populations
Basic science/biobanking	HPV strains, especially immune mechanisms/differences
Basic science/biobanking	Accessing some types of samples from biobanks could also be an issue
Basic science/biobanking	“Other anti-HPV therapies," e.g. immunotherapeutics, as these are not strictly antivirals, which implies drugs
Basic science/biobanking	Relight the idea that looking at replication and blocking it is a viable therapeutic approach to treating many HPV+ cancers
Basic science/biobanking	The one thing that was missing in the survey was models; There are a few PDX models out there now for HPV16+ OPSCC, and we are looking at these and demonstrating circular replicating genomes; therefore, we have the targets and we have a model to test them, but there are not many HPV+ OPSCC tumours available; most of them are provided by academic colleagues

The above comments were collated from a total of 7 responders. MSM, ■■■■■; PDX, ■■■■■; OPSCC, oropharyngeal squamous cell cancer. Colour coding for general themes is as previously (white = screening, light grey = vaccination and grey = basic science and biobanking).

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	Research Area	Priority	How to assess?	What do you perceive are the hurdles?	Plans for studies?	Funding Obtained?	Further Comments
Enter Y next to your research area of interest (can be more than one)		(1=highest, 10=lowest)	eg basic/mechanistic studies, RCTs, cohort studies, Popn level demonstration projects?	Governance, technical, funding etc	Yes, Maybe, No	Yes, Maybe, no	
	Oropharyngeal (OPSCC) cancer - molecular basis for differential survival outcomes						
	OPSCC screening strategies						
	Annotation of OPSCC to inform risk-based management						
	Treatment for OPSCC including de-escalation						
	Epidemiology and changing patterns of HPV associated disease (not cervix or OPSCC) including penile,vaginal, vuval cancer and recurrent respiratory papillomatosis						
	Impact of vaccine on HPV infection and associated disease						
	Immunogenicity of vaccines and long term protection						
	Collating the evidence for gender neutral vaccination						
	Primary disease prevention in LMIC via prophylatic vaccination (including 1 dose schedules)						
	Primary disease prevention in high income countires via prophylatic vaccination						
	Mangament of (and mitigation against) perceived safety issues with the HPV vaccine						
	Optimal cervical screening in high-income countires						
	Optimal cervical screening in low and middle income countires						
	Evidence based improvments for screening and disease management in the immunocompromised (HIV population, transplant recipients)						
	Self sampling to support cervical screening and disease management						
	Development and evaluation of HPV tests						
	Optimal screening strategies for vaccinated women						
	Exploring barriers to screening participation						
	Expoloring barriers to vaccination participation						
	Biomarkers for the risk stratification and triage of HPV infection						
	Application of biomarkers in screening programmes - challenges of implementation						
	Therapeutic vaccination						
	Anti-virals						
	Addressing/improving equity of access in cervical screening						
	Non-alpha and non-beta papillomaviruses						
	Beta-papillomaviruses						
	Animal papillomaviruses						
	Viral molecular and cellular biology - life cycle						
	Viral molecular and cellular biology - transformation						
	Viral molecular and cellular biology - other (not lifecycle or transformation)						
	Whole genome/Next generation sequencing						
	Quality assurance and metrics for HPV based screening						
	Epigenetics						
	Host virus interactions						
	HPV and the microbiome						
	HIV and other co-infections						
	HPV and CRISPR technology						
	Cervical cancer and inflammation						
	HPV assay and associated biomarker validation						
	Access to samples and optimal biobanking for the future						
	Health Communication						
	Health Policy Research						
	Cost effectiveness studies (primary and/or secondary disease prevention)						
	Health Behaviour						
	Childhood HPV infections & impact in adulthood						
	Mother to child HPV transmission						
	*For overlapping categories and for extra clarity please provide more details in **Comments**.						

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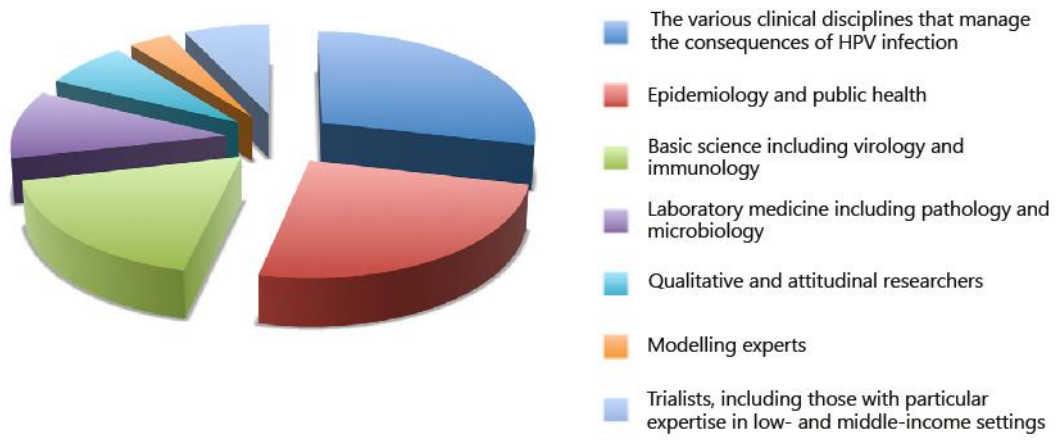

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